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Efficacy and Safety of Incremental Doses of Diltiazem for the Treatment of Stable Angina Pectoris

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The safety and efficacy of incremental doses of diltiazem in treating angina pectoris were assessed in 20 patients with functional class II to III exertional angina. During an initial single-blind dose titration phase, diltiazem produced a dose-related improvement in anginal frequency and exercise capacity. Weekly anginal attacks were reduced to 7.5 ± 8.9, 5.6 ± 7.8 and 4.9 ± 7.3 on diltiazem, 120, 240 and 360 mg per day, respectively, as compared with 11.9 ± 8.7 on placebo (all $p < 0.001$). Treadmill time was significantly enhanced by high dose (360 mg per day) as compared with moderate dose (240 mg per day) diltiazem: 473 ± 149 versus 424 ± 146 seconds ($p < 0.05$). Time to ischemic ST segment depression was similarly changed: 344 ± 132 versus 298 ± 142 seconds ($p < 0.05$) by high dose as compared with moderate dose diltiazem.

During a subsequent double-blind phase, high dose diltiazem significantly reduced weekly anginal frequency when compared with placebo: 3.1 ± 3.0 versus 9.3 ± 7.1 ($p < 0.001$); and increased treadmill exercise time: 508 ± 158 versus 418 ± 172 seconds on placebo ($p < 0.05$). Subjective and objective benefits of high dose diltiazem were sustained during a follow-up period of 6 months without major drug side effects.

Diltiazem, a calcium entry blocking agent, has been shown to be effective for the treatment of angina due to coronary spasm and obstructive coronary disease (1–14). Recent studies (5–12) demonstrated that diltiazem decreases the frequency of anginal attacks and improves exercise tolerance when given in doses up to 240 mg a day.

The present study was undertaken to evaluate the comparative efficacy, safety and tolerance of diltiazem when given in a higher daily dose of 360 mg to patients with exertional angina.

Methods

Study group. The study group consisted of 20 men, whose mean age was 58 years (range 43 to 67), enrolled from November 1981 through June 1982. All patients suffered from chronic stable angina and were in functional class II or III (15). Fifteen patients had coronary artery disease documented by coronary angiography or a prior myocardial infarction. None had symptoms suggestive of coronary vasospasm. Criteria for entry into the study required that each patient experience at least five episodes of angina per week in addition to demonstrating myocardial ischemia on exercise testing. The latter was defined as at least 1 mm of additional ST segment depression lasting 0.08 second after the J point, associated with exercise-induced angina, compared with the standing rest tracing. No patient had congestive heart failure, myocardial infarction within 3 months, valvular or congenital heart disease, thyrotoxicosis, anemia, noncardiac causes of chest pain or renal, hepatic or endocrine disease. All patients signed an informed consent form approved by the Institutional Review Board at Boston University Medical Center.

Study design. All antianginal medications were discontinued in each patient at least 48 hours before entering the study. Patients were allowed to consume nitroglycerin as needed for anginal attacks, but were instructed not to take any prophylactically.

The protocol consisted of a single-blind placebo-controlled dose titration phase (phase I), followed by a randomized double-blind crossover phase (phase II) and finally by an open label chronic phase (phase III) (Fig. 1). Patients were evaluated weekly during the first two phases and then during weeks 2, 4, 8, 16 and 24 of the third phase by the

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same study nurse and one of two physicians. Evaluation included a physical examination, electrocardiogram at rest, hematologic and biochemical profile, urinalysis and tabulation of frequency of anginal attacks and nitroglycerin consumption. Patient compliance was verified by counting study tablets and measuring blood levels.

Phase I consisted of a 2 week placebo period followed by a 3 week dose titration phase during which patients received diltiazem in daily doses of 120, 240 and 360 mg for 1 week each, respectively, in an attempt to ascertain the maximally tolerated dose for each patient. All patients tolerated the highest dose of diltiazem. The patients then received placebo for 1 week before entering the double-blind phase of the study.

Phase II was a 6 week randomized double-blind crossover phase during which either diltiazem, 90 mg, or placebo was given four times a day for 2 week periods. After each 2 week period, placebo was administered for a 1 week period. During phase III, each patient continued the daily 360 mg diltiazem dose for 6 months.

Exercise testing. Ten treadmill exercise tests were performed during the 12 weeks of phases I and II, and four additional tests were performed during phase III using a modification of the Bruce protocol (Fig. 1). A 3 minute warm-up stage (1.7 mph and 5% grade) was followed by the standard Bruce protocol (16). A 12 lead electrocardiogram was recorded at rest and at 1 minute intervals during exercise and recovery until the ST segments and heart rate resembled the baseline tracing. Blood pressure was recorded at rest, at the end of each stage of exercise, at the onset of angina and during recovery. The patients exercised to a symptom-limited end point consisting of either moderate angina, dyspnea or fatigue.

Variables analyzed on the exercise tests included: total exercise time, time to onset of angina, time to 1 mm of additional ST depression and heart rate, blood pressure and rate-pressure product at rest, at the end of the first 3 minutes of exercise (submaximal) and at maximal exercise. All tests were performed 2 hours after the last dose of study medication was administered.

Blood levels. Diltiazem blood levels were determined weekly during phase I. Blood samples were drawn 2 hours after administration of the last dose of study medication. Plasma diltiazem concentration was measured by gas chromatography (17).

Statistical analyses. A one-way analysis of variance for repeated measures was used to determine if there were significant differences in the group mean values. If the analysis of variance indicated a significant difference, a two-tailed, paired Student's *t* test was then applied to the data. Probability (p) was considered significant at the < 0.05 level. All values are expressed as mean ± 1 standard deviation.

Results

Blood levels and dosage of diltiazem. Mean plasma levels during treatment with 120, 240 and 360 mg per day were 93 ± 35, 183 ± 63 and 274 ± 102 ng/ml, respectively ($p < 0.001$). A five-fold difference in the plasma levels was observed after a given dose. Diltiazem levels did not correlate with improvement in exercise tolerance or decrease in anginal frequency.

Effect on angina (Table 1). Anginal frequency during the single-blind phase was significantly reduced by 41, 59 and 61% during treatment with 120, 240 and 360 mg per day of diltiazem, respectively ($p < 0.001$ compared with placebo for all doses). During the double-blind phase, anginal attacks were decreased by 66% when patients were taking diltiazem, 360 mg per day ($p < 0.001$). Similarly, the number of nitroglycerin tablets required per week decreased significantly with all doses of diltiazem.

Effect on hemodynamics (Table 1). The mean heart rate at rest was 87 ± 16 beats/min when the patients were taking placebo during the single-blind phase. Diltiazem in doses of 240 and 360 mg/day resulted in a reduction of heart rate to 79 ± 14 and 80 ± 14 beats/min, respectively ($p < 0.05$). During the double-blind phase, the heart rate at rest was likewise reduced by diltiazem. The systolic blood pressure at rest was significantly altered only by the highest dose of diltiazem during the single-blind phase. When the rate-pressure product was analyzed, both 240 and 360 mg per day caused a significant reduction in the rate-pressure product.

The heart rate and rate-pressure product during submaximal exercise were measured to be significantly less with

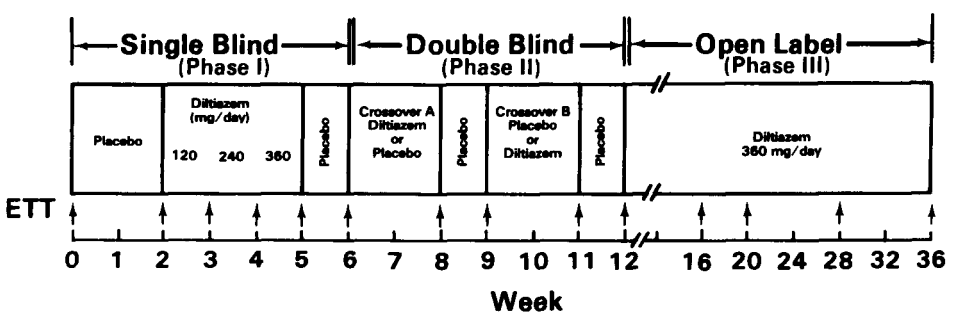


Figure 1. Protocol design. ETT = exercise treadmill test.

Table 1. Results of the Single-Blind and Double-Blind Crossover Comparison

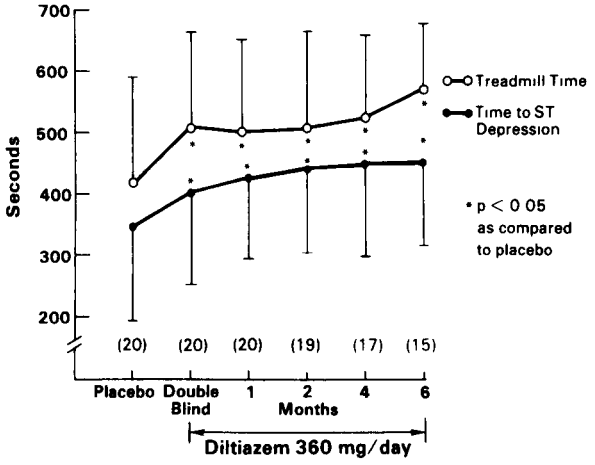
	Single-Blind				Double-Blind	
		Diltiazem				
	Placebo	120 mg/day	240 mg/day	360 mg/day	Placebo	Diltiazem 360 mg/day
Anginal episodes per week	11.9 ± 8.7	7 5 ± 8.9†	5.6 ± 7 8†	4.9 ± 7.3†	9.3 ± 7.1	3.1 ± 3.0†
Nitroglycerin tablets per week	8.4 ± 8.7	5.5 ± 8.8‡	3.8 ± 7 7‡	3.9 ± 7.2†	5.9 ± 5.2	1.7 ± 2.4‡
Treadmill time (seconds)	320 ± 159	397 ± 159†	424 ± 146†	473 ± 149†.	418 ± 172	508 ± 158‡
ST segment deviation						
Onset (seconds)	244 ± 115	303 ± 147‡	298 ± 142	344 ± 132†.	347 ± 153	404 ± 153‡
Peak (mm)	1.6 ± 1 0	1.5 ± 1.0	1 6 ± 1.2	1 7 ± 1 1	1.8 ± 1.2	1.7 ± 1.2
Heart rate (beats/min)						
Rest	87 ± 16	84 ± 15	79 ± 14‡	80 ± 14‡	84 ± 17	75 ± 13†
Submaximal exercise	108 ± 15	103 ± 14‡	101 ± 14†	97 ± 15†.	102 ± 18	93 ± 14†
Peak exercise	122 ± 21	119 ± 20	120 ± 17	120 ± 18	123 ± 20	117 ± 18‡
Systolic blood pressure (mm Hg)						
Rest	137 ± 19	130 ± 11	130 ± 11	128 ± 11†	127 ± 16	126 ± 12
Submaximal exercise	161 ± 20	149 ± 15‡	145 ± 15‡	143 ± 13‡	146 ± 18	143 ± 14
Peak exercise	174 ± 24	169 ± 19	167 ± 21†	160 ± 21†	163 ± 25	162 ± 21
Rate-pressure product (beats/min · mmHg · 10^{-2})						
Rest	119 ± 32	110 ± 24	103 ± 23‡	103 ± 19‡	107 ± 23	95 ± 18‡
Submaximal exercise	174 ± 38	154 ± 32‡	146 ± 28†	138 ± 29†.	149 ± 39	134 ± 28‡
Peak exercise	215 ± 58	203 ± 51	201 ± 42	192 ± 41	206 ± 51	190 ± 32‡
Time to angina (seconds)	241 ± 143	335 ± 176†	350 ± 135†	379 ± 185†	349 ± 179	416 ± 189‡

*$p < 0.05$ vs. next lower dose of diltiazem. †$p < 0.001$ vs. placebo ‡$p < 0.05$ vs. placebo

all doses of diltiazem during the single- and double-blind phases. At peak exercise, the heart rate and rate-pressure product produced were reduced only during the double-blind phase. The systolic blood pressure at submaximal and maximal exercise was only reduced during the dose titration period (phase 1).

Exercise performance (Table 1). Treadmill time was significantly increased by diltiazem: 33% on 120 mg per day, 50% on 240 mg per day and 67% on 360 mg per day, as compared with placebo ($p < 0.001$). A similar improvement (38%) was observed during the double-blind phase. The time to onset of angina and onset of ST segment depression was significantly prolonged in both the single-blind and double-blind phases of the protocol.

Figure 2. Treadmill exercise time and time to ST segment depression during the double-blind and open label phases of the study. Values are expressed as mean ± standard deviation. Numbers in parentheses represent the number of patients evaluated.



Electrocardiographic effects. The PR interval at rest increased from 157 ± 24 ms on placebo to 167 ± 25, 168 ± 23 and 173 ± 26 ms on 120, 240 and 360 mg per day diltiazem, respectively ($p < 0.01$). No significant changes in the QRS or QT intervals were observed. The amount of ST segment depression at peak exercise was unaffected by diltiazem (Table 1).

Comparison of various dosages of diltiazem. Increasing doses of diltiazem resulted in additional reductions in anginal attacks and nitroglycerin consumption and improvement in exercise tolerance. When the 360 mg daily dose of diltiazem was compared with the 240 mg daily dose, the heart rate and rate-pressure product were significantly reduced during submaximal exercise (Table 1). When diltiazem was increased from 240 to 360 mg per day, both the onset of ST segment depression and the total treadmill time were significantly prolonged, with the majority of patients (85%) demonstrating a further increase in treadmill time, and nine patients (45%) showing both an increase in treadmill time and a decrease in the number of anginal attacks.

Effects of placebo (Table 2). During phases I and II of the study, each patient underwent a total of 10 exercise tests. One was performed just before entry into the study (the control test) and five other tests were performed while

the patient was taking placebo (Fig. 1). There were no differences in any of the variables measured between the control exercise test and the initial placebo test. However, when the first placebo evaluation was compared with the last, there was a significant decrease in the number of anginal attacks and the submaximal rate-pressure product, and an increase in treadmill time and onset of ST segment depression was observed.

Adverse reactions. All doses of diltiazem were extremely well tolerated. Two patients had transient flushing, two had mild pedal edema and four developed first degree atrioventricular block (PR interval = 0.20 to 0.22 second). No side effect was severe enough to necessitate a reduction in the dosage or discontinuation of the medication.

Long-term follow-up. Twenty patients were maintained on diltiazem, 360 mg per day, after completion of the first two phases of the study. One patient dropped out of the study after 4 months of open label drug therapy because of the development of unstable angina requiring additional medication. Three patients were withdrawn because they underwent elective coronary bypass surgery in accordance with the preference of their referring physicians, despite continued good clinical response to diltiazem. One other patient refused to take medication because of the disappearance of his anginal symptoms.

Treadmill testing on the patients remaining in the study demonstrated a persistent increase in treadmill time and time to ST depression (Fig. 2). No new adverse drug response was noted at any time during the follow-up phase.

Discussion

Effectiveness of diltiazem therapy. Diltiazem has been used extensively with good efficacy for the treatment of vasospastic angina (1–4,18). Several studies (5–14) recently reported on its efficacy for exertional angina. Using a single dose of 90 mg of diltiazem, one group demonstrated a prolonged time to angina and ST depression (14), and two other studies using 120 mg doses have shown beneficial effects (13,19). Two multicenter clinical trials (7,12) evaluating the efficacy of diltiazem have been reported recently. Both trials using doses of 240 mg per day demonstrated that diltiazem prolonged exercise time, time to angina and time to ST depression compared with placebo and had mild infrequent side effects.

We found that 360 mg per day was well tolerated. Although the clinical response to this dose was similar to the 240 mg per day dose, most of our patients had a further increase in exercise time and time to ST segment depression compared with the more frequently studied dose of 240 mg per day. This effect was persistent during the follow-up period of 6 months without major side effects. One recent study (20) also found subjective and objective improvement with three different doses of diltiazem as compared with placebo; the best reduction of anginal attacks and enhancement of exercise capacity was observed with a 360 mg per day dose.

Mechanism of antianginal effect. The results of this study provide insight into the mechanism of action of diltiazem in patients with exertional angina. When the patients were taking diltiazem, they generally exercised longer and had a lower rate-pressure product at rest and throughout exercise. This suggests that the antianginal effect of diltiazem could be explained by a reduction in myocardial oxygen demand at a given external work load. Diltiazem also caused a significant reduction of the heart rate at rest, but none of our patients demonstrated severe bradycardia.

Plasma diltiazem levels varied greatly after a given dosage, which may be attributable to its variable liver metabolism. This high interpatient variability probably caused the lack of correlation between blood levels and response, although the mean blood levels increased concomitantly with increasing dosages.

Table 2. Effects of Placebo on Clinical and Exercise Performance

	Control	Placebo					p Value
	Week 0	Week 2	Week 5	Week 7 or 11	Week 9	Week 12	Week 2 vs. 12
Anginal episodes per week	10.4 ± 3.7	11.9 ± 8 7	10 4 ± 8.2	9 3 ± 7.1	10 5 ± 8 3	8.2 ± 9.0	< 0.05
Nitroglycerin tablets per week	7.9 ± 3 5	8.4 ± 8.7	7.3 ± 7.9	5.9 ± 5.2	7.8 ± 8.6	5.4 ± 7.8	NS
Treadmill time (seconds)	306 ± 118	320 ± 159	330 ± 162	418 ± 172	373 ± 172	403 ± 185	< 0.01
Onset of ST depression (seconds)	230 ± 115	244 ± 115	254 ± 142	347 ± 153	311 ± 165	328 ± 164	< 0.01
Rate-pressure product (beats/min • mm Hg • 10^{-2})							
Rest	121 ± 35	119 ± 32	119 ± 28	107 ± 23	110 ± 23	109 ± 26	NS
Submaximal exercise	177 ± 57	174 ± 38	159 ± 44	150 ± 39	150 ± 35	148 ± 30	< 0.001
Maximal exercise	217 ± 57	215 ± 58	195 ± 56	206 ± 51	201 ± 47	206 ± 47	NS

NS = not significant.

Effect on exercise performance. Multiple exercise testing can lead to enhanced exercise performance, as has been shown in our study and others (6,21–23). Although the baseline control exercise test was not different from the first placebo test, there was an increase in the treadmill time and onset of ST segment depression and a decrease in the submaximal rate-pressure product when the last placebo test was compared with the first. Several explanations may account for these changes. Increasing familiarity of the patients with the equipment and exercise protocol may lead to enhanced exercise capacity. In addition, a drug carryover effect may have been observed, as several of the placebo tests occurred 1 week after diltiazem was discontinued. Finally a training effect from repeat exercise tests may have occurred—this is suggested by the decrease in the submaximal rate-pressure product. Despite these effects, diltiazem caused an additional 63% reduction in anginal attacks and a 22% increase in treadmill time compared with the best values on any of the placebo tests.

Limitations of study. The results of this study should be interpreted on the basis of certain limitations inherent in the study design. First, the comparisons among the different doses could only be performed during the single-blind phase. The patients also received more study tablets while receiving the higher doses. Second, patients were maintained on each incremental dose for a single week, which conceivably could have prevented the full effect of that particular dose. Finally, a "training effect" cannot be ruled out as a contributing factor to the increased exercise tolerance observed during increasing doses of diltiazem.

Implications. We conclude that diltiazem is an effective agent in the treatment of exertional angina. Our study suggests that in patients whose response to 120 mg per day is suboptimal, the dose can be safely increased to 240 or 360 mg per day with the expectation of added beneficial effects.

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